UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/620,820 | 07/21/2000 | Alan D. Attie | 960296.97290 | 4397 |

7590 08/15/2006

Nicholas J. Seay
Quarles & Brady LLP
P O Box 2113
Madison, WI 53701-2113

| EXAMINER | |
|---|---|
| QIAN, CELINE X | |
| ART UNIT | PAPER NUMBER |
| 1636 | |

DATE MAILED: 08/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/620,820 | ATTIE ET AL. | |
| | Examiner | Art Unit | |
| | Celine X. Qian Ph.D. | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *19 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *13-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 July 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Claims 1-17 are pending in the application. Claims 13-16 are withdrawn from consideration for being directed to non-elected subject matter. Claims 1-12 and 17 are currently under examination.

This Office Action is in response to the amendment filed on 5/19/06.

### *Response to Amendment*

The declaration filed on 5/19/06 is sufficient to overcome the rejection of claims 1-12 and 17 based upon 35 U.S.C. 103 (a).

Claims 1-12 and 17 are rejected under 35 U.S.C. 112 1st paragraph for reasons given below.

### *New Grounds of Rejection*

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12 and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not

limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

The nature of the invention is a method of lowering serum cholesterol or triglyceride in an individual comprising the step of making a genetic construct comprising (1) a protein coding sequence encoding for the expression of a fusion protein including a low density lipoprotein receptor without the native membrane binding domain, and a localization domain which directs localization of the fusion protein to the interior of a cell in the individual, and (2) a promoter effective in the cells of the individual to express the protein encoding sequence; and delivering the genetic construct into the individual. In the example given in the specification, applicants disclose a fusion protein encoding a truncated soluble LDLR, LDLR354, linked to an endoplasmic reticulum (ER) localization sequence, KDEL, which is capable of decrease hepatic apoB secretion both *in vitro* and *in vivo*. The specification further discloses that serum LDL is lowered when this construct is injected through tail vein of the mice.

The breath of the claims is broad. The broadest claim is drawn to a method of lowering serum cholesterol by making a construct comprising a nucleic acid encoding a fusion protein comprising (1) a protein coding sequence encoding for the expression of a fusion protein including a low density lipoprotein receptor without the native membrane binding domain, and any localization domain which directs localization of the fusion protein to the interior of a cell in the individual, and (2) a promoter effective in the cells of the individual to express the protein

encoding sequence; and delivering the genetic construct into any type of mammal including human.

The teaching of the specification is limited. The specification teaches that introduction of a fusion protein of LDLR354 and KDEL into primary hepatocytes results in the decrease of secretion of apoB lipoproteins. The specification also teaches that administering a plasmid vector encoding a fusion protein of LDLR354 tagged with KDEL to the tail vein of the mouse result in decreased plasma LDL in 48 hours post administration. However, the specification fails to teach whether such decrease of LDL can be sustained over longer period of time. The specification also fails to teach whether such effect may be achieved in other animal models or human. Although the claims are directed to a method of lowering serum cholesterol in a mammal, the specification clearly teaches that the method is implicated in treating human hypercholesterolemia (see pages 1 to 2). Thus, the enablement is analyzed based on such standard.

The state of art at the time of filing considers the success of gene therapy as unpredictable. Verma et al. (1997, Nature, Vol. 389, pages 239-242), Anderson et al.(1998, Nature, Vol. 392, pages 25-30), and Palu et al.(1999, Journal of Biotechnology, Vol. 68, pages 1-13) discuss the inherent difficulties in gene therapy. The major difficulties include poor delivery systems and poor gene expression after delivery (see Anderson, page 30, 1st col., 5th paragraph). Another factor that affects the efficacy of gene therapy methods is the immune system of the host organism (see Palu, page 9, 1st col., 2nd paragraph, lines 1-5). The host immune system rejects the foreign cell that is introduced to said host thus prevents the expression of the gene within the cell. In fact, in the response filed on 5/19/06, Applicants also acknowledge that the success of *in*

*vivo* gene therapy remains unpredictable due to difficulties such as shortcoming in gene delivery systems and inadequate understanding of the biological interaction of delivery systems with target cells. Although Applicants have demonstrated that delivering a plasmid construct encoding LDLR354 and KDEL can lower LDL level in a mouse deficient of LDLR 48 hours post injection, whether such treatment would result in any therapeutic response in human is still unpredictable because the specification fails to demonstrate whether sustained expression may be maintained at sufficient level to lower LDL for longer period of time. In the review written by Gotthardt and Schuster, the authors indicate that data from animal experiments, as well as results of the clinical protocol clearly demonstrate we are still at the beginning stage of the process of improving vector systems and understanding the interfering with the reactions of the organism against gene delivery and expression (see page 359, 2nd paragraph). This article also indicates that early experiments of gene transfer results in restored cholesterol level to near normal in Watanabe rabbit, however, it only lasted for a few weeks. The article concludes that major obstacles must still be overcome before gene therapy for FH becomes a reality because the current transfer system have neither the ability to effect stable gene transfer and expression nor do they allow for repeated application. Moreover, another major obstacle of gene therapy is the safety of gene delivery. In 2005, 5 years after the effective filing date of the instant application, a third child who underwent gene therapy treatment developed cancer as a result, which suggest that long term risk is a serious factor in gene therapy (see article by Rich Weiss).

While the instant specification demonstrates some effects in lowering plasma LDL in the mouse model, it fails to address the art-recognized problem as discussed above. The specification neither demonstrates sustained effect of the fusion construct in lowering plasma

LDL, nor does it demonstrate that such treatment is safe. Thus, based on the limited disclosure based on the instant specification, it at most enables a method of lowering LDL in a mouse model, which does not extend the predictability to other mammals including human. Therefore, in view of the limited teaching of the specification and high level of unpredictability existed in the relevant art, one skilled of art would have to engage in undue experimentation to practice the method as claimed. Thus, the claimed method is not enabled by the instant specification.

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X. Qian Ph.D. whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Celine X Qian Ph.D.
Examiner
Art Unit 1636

CELINE QIAN, PH.D.
PRIMARY EXAMINER